(12) UK Patent Application (19) GB (11) 2 025 975 A

(21) Application No 7922098
(22) Date of filing 25 Jun 1979
(23) Claims filed 25 Jun 1979
(30) Priority data
(31) 25853
(32) 19 Jul 1978
(33) Italy (IT)
(43) Application published
30 Jan 1980
(51) INT CL³
C07F 9/38 A61K 31/66
(52) Domestic classification
C2P 3B13 3B14A 3B21 5A
7 A1 A
(56) Documents cited
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Chemical Abstracts
Eighth Collective Femula
Index (1967—1971)
$C_3H_7O_4P$ pp 481F—482F
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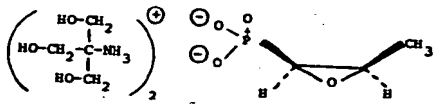
(54) Fosfomycin Derivative

(57) Bis-(2-ammonium-2-hydroxymethyl-1,3-propanediol)-(2R-cis)-(3-methyloxiranyl)phosphonate of the formula:



inhibits the growth of gram-positive and gram-negative bacteria. It can be prepared by a double exchange reaction between the corresponding phosphonic acid or salt and the corresponding propanediol or salt.

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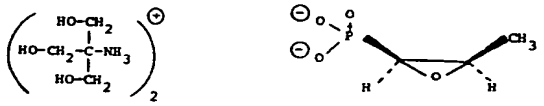
SPECIFICATION

Fosfomycin Derivatives

The present invention relates to fosfomycin derivatives, that is a new salt of (2R-cis)-(3-methyloxiranyl)phosphonic acid and the preparation thereof.

The new salt of the invention is bis-(2-ammonium-2-hydroxymethyl-1,3-propanediol) (2R-cis)-(3-methyloxiranyl)phosphonate of the formula



(2R-cis)-(3-methyloxiranyl)phosphonic acid is also known as Fosfomycin (Merck Index-9th Edition-4110). Fosfomycin sodium and calcium salts are widely used in human and veterinary fields to inhibit the growth of gram-positive and gram-negative pathogenous bacteria. The fosfomycin salt of the invention shows a tolerability and a bioavailability remarkably more favourable than those of fosfomycin sodium and calcium salts. The bioavailability of the fosfomycin salt of the invention in man is at least 200% (i.e. double) that of the sodium and calcium salts of fosfomycin in terms of both cumulative urinary recovery active antibiotic and area under the blood level vs. time curve.

The invention includes pharmaceutical compositions comprising bis-(2-ammonium-2-hydroxymethyl-1,3-propanediol) (2R-cis)-(3-methyloxiranyl)phosphonate in admixture with one or more therapeutically acceptable binding agents, excipients and/or carriers.

The preparation of the fosfomycin salt of the invention may be carried out according to the methods generally used in chemistry and known in the art. For instance, it may be prepared by a double exchange reaction between the monohydrated calcium salt of the (2R-cis)-(3-methyloxiranyl)phosphonic acid and the oxalate of the 2-amino-2-hydroxymethyl-1,3-propanediol.

Example

To 105.9 g of the monohydrated calcium salt of (2R-cis)-(3-methyloxiranyl)phosphonic acid suspended in 320 ml water at 60°C and stirred, a solution of 145 g of 2-amino-2-hydroxymethyl-1,3-propanediol and 49 g of oxalic acid in 270 ml water was gradually added. The suspension was allowed to cool to room temperature while the stirring was continued for seven hours. After standing overnight at 4°C with stirring, the suspension was filtered off under vacuum on Theorite 5 (trademark of Seitz-Filter-Werke for filter material) and the filtrate was evaporated to dryness. The residue was treated with 500 ml of absolute ethyl alcohol and refluxed with stirring for one hour. The white crystalline product which separates after cooling was collected by filtration under vacuum and dried for 10 hours at 60°C under vacuum. 185 g of bis-(2-ammonium-2-hydroxymethyl-1,3-propanediol) (2R-cis)-(3-methyloxiranyl)phosphonate were thus obtained.

m.p.=146—148°C.

Elementary analysis gave the following results:

for $C_{11}H_{29}N_2O_{10}P$

	C	H	N
found %	34.55	7.64	7.20
calculated %	34.74	7.69	7.37

$[\alpha]_D^{20}=-3.3°$ (c=10%).

Claims

1. Bis-(2-ammonium-2-hydroxymethyl-1,3-propanediol)-(2R-cis)-(3-methyloxiranyl)phosphonate.

2. A process for the preparation of bis-(2-ammonium-2-hydroxymethyl-1,3-propanediol)-(2R-cis)-(3-methyloxiranyl)-phosphonate in which (2R-cis)-(3-methyloxiranyl) phosphonic acid or a salt thereof is reacted with 2-amino-2-hydroxymethyl-1,3-propanediol or a salt thereof by a double exchange reaction.

3. A process for the preparation of bis-(2-ammonium-2-hydroxymethyl-1,3-propanediol) (2R-cis)-(3-methyloxiranyl)phosphonate as herein described in the Example.

4. A pharmaceutical composition comprising bis-(2-ammonium-2-hydroxymethyl-1,3-propanediol) (2R-cis)-(3-methyloxiranyl)phosphonate in admixture with one or more therapeutically acceptable binding agents, excipients and/or carriers.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1980. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.